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Immunological and Pathophysiological Mechanisms of Systemic Inflammation

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ABSTRACT

General characteristics of systemic inflammation as a typical pathological process. Inflammation is a universal and common type of pathological the process underlying most of the known human diseases. The essence of inflammation is the body's reaction to local damage, which is aimed at isolating and eliminating the damaging factor, and then tissue regeneration. The reaction develops mainly locally – in the focus of inflammation. The main functional role in the focus of inflammation is played by inflammatory infiltrate cells – various types of leukocytes and mobile macrophages. In turn, the reaction of microvessels, the hemostasis system, mastocytes and many other types of stromal cells ensures the migration of effector cells to the focus of inflammation, as well as the localization of damaging agents. The type of inflammatory process – exudative-destructive inflammation (purulent) or various variants of productive inflammation, as well as the final effectiveness of the inflammatory process as a whole depends on the composition of the inflammatory infiltrate cells and the nature of their relationship. The implementation of effector mechanisms in the focus of inflammation cannot be carried out without "resource support" from the whole organism. This task is mainly solved by a systemic inflammatory reaction, which includes a number of interrelated processes: stress response of the neuroendocrine system, primarily the hypothalamic-pituitary-adrenal complex; generalized manifestations of the immune response, acute phase response of the liver, increased leukocytopoiesis in the bone marrow. The main initiating mechanism for the development of a systemic inflammatory reaction is the entry of individual cytokines and some other inflammatory mediators into the systemic bloodstream from the focus of inflammation. The need for it does not arise with any, but only with a pronounced inflammatory process, with a high level of expenditure of metabolic and cellular resources. Manifestations of a systemic inflammatory reaction are diverse: fever, neuromuscular asthenia, an increase in blood glucose and other energy substrates, leukocytosis, an increase in acute phase proteins in the blood and other adaptive changes in homeostasis. Thus, the systemic inflammatory reaction has both common and different manifestations from other stress variants at the level of the whole organism. In general, the inflammatory process includes two complementary genetically determined programs in relation to the focus of inflammation: "internal" – at the local level and "external" – systemic inflammatory response. Like any other protective mechanism for the body, individual manifestations of inflammation can in certain cases have negative consequences, which, however, does not negate the expediency of inflammation as a protective process for the body as a whole. Knowledge of the general patterns of the inflammatory process allows us to understand the pathogenesis of a wide range of inflammatory diseases. Meanwhile, there are pathological processes directly related to the involvement of "inflammatory" mechanisms, the pathogenesis of which is difficult to describe, and in some cases impossible from the standpoint of traditional (classical) ideas about inflammation. This applies, first of all, to the most life–threatening forms of pathology - shock states, acute manifestations of multiple organ failure, the development of disseminated intravascular coagulation syndrome and some other critical human conditions. Very often, the role of the focus of inflammation in these conditions is insignificant, and in some cases it (the focus) is completely absent. Practitioners were the first to note the connection between the development of critical conditions in humans with "inflammatory" mechanisms in sepsis, and then non-infectious processes. At the same time, two out of four possible criteria are sufficient to verify a systemic inflammatory reaction. The use of criteria for systemic inflammatory response in clinical practice allowed us to identify a risk group for severe complications. "Inflammatory" mechanisms, which are characterized by signs of a systemic inflammatory reaction, are generally adaptive in nature and cannot directly determine the pathogenesis, for example, of a shock state. All this predetermined the need to describe the model of systemic inflammation as an independent typical pathological process, related, but not identical to classical inflammation, which requires the separation of the designated two alternative typical pathological processes. To this end, we will pay attention to the origins of the inflammatory reaction. Any cell is capable of responding to the effects of a damaging factor, this response can be referred to as cellular stress. Meanwhile, the damaging factors themselves are heterogeneous.

Firstly, these are various micro defects of cellular structures and changes in vital environmental parameters, such as hypoxia, disturbances of acid-base balance and temperature regime; parasitization by viruses and other intracellular organisms. All these factors are capable of damaging the cell directly and are damaging agents by definition. Secondly, it is the effect on the cell, or rather on cellular receptors, of molecules carrying information about the possibility of damage. These molecules "warn" the cell about the presence of microorganisms or other factors that pose a potential danger.

KEYWORDS: *So, the development of inflammatory reactivity can be considered from the perspective of cellular stress, which solves two main tasks*

1. increasing the resistance of the cell to the action of damaging factors of various nature;

2. formation of intercellular cooperation during the development of the inflammatory response program.

The mechanisms of anti-inflammatory resistance can be reduced to the following components.

1. The presence of a certain threshold of response to the action of damage factors – the cell ignores pre-threshold stimuli.
2. Removal of bacterial antigens and tissue degradation products from the systemic bloodstream due to inactivated phagocytosis by vascular stromal macrophages.
3. Blocking of the initial systemic manifestations of the "internal" mechanisms of the inflammatory response from the antiproteinase and antioxidant systems of the body, inhibitors of individual components of hemostasis and complement systems and other anti-inflammatory mechanisms.

Thus, for the development of systemic inflammation, the generalized effect of damaging factors should exceed the compensatory capabilities of anti-inflammatory resistance factors in terms of the strength of the effect. In general, systemic cellular stress is a kind of background on which systemic inflammation develops.

However, the inflammatory process cannot be represented only as a reaction of individual cells without highlighting the key and secondary mechanisms of intercellular interrelation. From these positions, systemic inflammation can be characterized as a generalized involvement of the "internal" program of the inflammatory process. However, it is impossible even to imagine the human body as a "large focus of inflammation". It is obvious that the generalization of the basic mechanisms of inflammation at the systemic level will obey the same patterns of intercellular interaction, but they must manifest themselves in some other way. With the development of any variant of inflammation, the "internal" program of the focus functions as a whole, although the specific role of its individual components is variable. In general, as already noted, in classical inflammation, the main cellular elements of these mechanisms are leukocytes and mobile macrophages of the inflammatory infiltrate. On the contrary, with systemic inflammation, the dominant force involved in the "inflammatory" transformation is about three kilogram mass of endotheliocytes of the adult human body, as well as macrophages-residents of parenchymal microvessels organs, for example, stellate liver cells (Kupfer cells). This circumstance determines the relative specificity of systemic inflammation as a typical pathological process, since a high degree of diversity of manifestations of classical inflammation is determined by the characteristics of not only the damaging factor, but also the damaged organ, as well as numerous variants of cellular composition and intercellular interactions in the focus of inflammation. Thus, the central link in the development of systemic inflammation is the vascular reaction, or, in other words, systemic "inflammatory" microcirculation, which is clinically manifested in the form of life-critical microcirculatory disorders.

The reaction of micro vessels includes:

- paralysis of contractile function of smooth muscle cells of arterioles and precapillary sphincters;
- adhesion on the endothelium, mainly postcapillary venules, activated phagocytes secreting various cytotoxic ingredients – hydrolases, free radicals, cationic proteins;
- changing the shape of endotheliocytes and the formation of "gaps" between them, micro thrombosis in post capillary venules, free transfer of plasma proteins from these micro vessels to the extravascular environment;
- violation of oxygen transport and other metabolic processes between the extravascular and intravascular environment at the level of the capillary network;
- pathological activation of complement in the intravascular environment with the formation of anaphylaxines (C3a and C5a), as well as the kallikrein-kinin system;
- development of destructive processes of paravascular connective tissue and parenchymal cells of all vital internal organs.

The apotheosis of microcirculation disorders is a violation of microhemodynamics in the form of shock resistant to vasopressor therapy and infusion of blood substitutes. In other words, with systemic inflammation, a systemically involved "internal" mechanism that determines the development of an exudative vascular reaction in the focus of inflammation comes to the fore.

Systemic inflammation is a typical, multisyndromic, phase–specific pathological process that develops with systemic damage and is characterized by a general inflammatory reactivity of endotheliocytes, plasma and cellular factors of blood, connective tissue, and in the final stages - microcirculation disorders in vital organs and tissues. The main phenomena of systemic inflammation are primary and secondary systemic changes with insufficient anti-inflammatory resistance factors, microcirculation disorders against the background of systemic development of "inflammatory" cellular stress. The main initiating factor in the development of organ dysfunction is a violation of oxygen transport, as a consequence of hemodynamic disorders. Since the indicated changes occur systematically, but not to the same extent in different target organs, the clinical picture of systemic inflammation is diverse, usually this or that combination of "resuscitation" syndromes.

The main types of inflammation are: the central nervous system, lungs, heart, liver, kidneys, adrenal glands, i.e. all vital organs with a high density of the vascular network. An important point for understanding the dynamics of systemic inflammation is a clear understanding of the initial, especially reversible stages of its development. It is possible to distinguish two fundamentally different variants of the development of systemic inflammation – "pushing through" and "breakthrough". In the "pushing" variant, the transition from classical to systemic inflammation occurs gradually, the factors of alteration overcome at the systemic level, barriers of anti–inflammatory resistance for several days with the formation of a "gray zone" - presystemic inflammation, i.e. a condition in which it is impossible to clearly confirm or deny the presence of systemic inflammation. The "pushing through" option is characteristic of the development of sepsis and some gradually developing traumatic processes. Directly systemic inflammation as an integral process combines several phenomena (more particular processes) reflecting a generalized the involvement of the "internal" mechanisms of the inflammation program, which include:

- generalized inducible production of cytokines and other regulatory stress molecules;
- intravascular activation of complement and various types of leukocytes;
- disseminated intravascular coagulation of blood;
- systemic degranulation of mast cells;
- systemic microcirculatory disorders and related multiple organ dysfunction, the apotheosis of which is severe vascular shock.

In turn, these processes can lead to the development of the phenomenon of secondary systemic al- this makes the process of systemic inflammation difficult to reverse. The main direct causes of secondary systemic alteration include the following processes:

- hypoxia, which develops as a result of impaired oxygen transport;
- systemic acidosis: metabolic (accumulation of lactate and other organic acids in the blood) and gas (accumulation of carbon dioxide in case of respiratory insufficiency);
- secondary endotoxicosis (accumulation of endotoxin in the blood of gram-negative bacteria and other microbial patterns of alteration, due to impaired function of barrier tissues);
- metabolic stress syndrome (accumulation of higher fatty acids in the blood against the background of a sharp decrease in the ligand-binding ability of albumin; unbound higher fatty acids form micelles in the blood that damage the membranes of endotheliocytes and activate the contact factor of blood clotting);
- hypovolemia (insufficiency of the total volume of circulating blood to realize the function of macrohemodynamics); - accumulation of tissue breakdown products in the blood.

With the "provyv" variant, the buffer system of anti-inflammatory resistance is overcome with lightning speed by the powerful influence of the damaging factor. In this case, the stage of presystemic inflammation is several hours – the time required to involve the expression products of inducible genes in the process, and preventing the development of systemic inflammation is a more difficult task than with the "pushing" option.

In the "breakthrough" variant, the focus of classical inflammation may be absent or its significance for the development of systemic inflammation

Examples of the development of systemic inflammation of the "breakthrough" type:

- the most critical variants of acute, rapidly developing traumatic lesions of various nature;
- lightning sepsis in humans or experimental generalized Schwartzman phenomenon in animals;
- hemotransfusion shock or other causes of massive intravascular hemolysis;
- anaphylactic shock;
- crash syndrome (prolonged compression syndrome, which develops after the restoration of blood supply in the squeezed limb);
- the action of biological poisons that uncontrollably activate hemostasis or complement systems in the intravascular environment;
- amniotic fluid embolism – the effect of tissue factor (tissue thromboplastin) on the hemostasis system in the intravascular environment.

Phases of development of systemic inflammation. The 1st phase is the phase of the development of systemic inflammation (marginal) with the "pushing" variant corresponds to the concept of presystemic inflammation, or, in other words, the "gray zone" during the transformation of classical inflammation into systemic inflammation. The duration of the phase in this the case may be approximately from one to several days. During this time, agents of systemic damage overcome the resistance of anti-inflammatory resistance factors. In the "provyv" variant, the duration of the phase is from 2 to 12 hours and is determined by the rate of involvement in the systemic process of the products of inducible genes responsible for the implementation of the basic mechanisms of the inflammation program. This dynamic is determined by the lightning-fast nature of overcoming the barriers of anti-inflammatory resistance on the part of damage agents. The 2nd phase – primary phlogogenic shock (hyperergic) – is characterized by hypercytokinemia: a sharp increase (hundreds and thousands of times) in the blood of both pro-inflammatory (IL-1β, IL-6, IL-8, IL-12, GM-CSF, TNFa) and conditionally anti-inflammatory (IL-10, IL-1ra) cytokines. The levels of systemic inflammatory response corresponding to UR-4-5 determine mainly the systemic nature of the production of stress molecules. The phase is also associated with other manifestations of generalization of "internal" mechanisms. The second phase is characterized by the dominance of the 2nd stage of cellular stress at the systemic level. The 3rd phase – depressive (hypoergic) – is characterized by a relatively low level of cytokinemia, from both pro- and anti-inflammatory cytokines. The development of oxidative stress is less pronounced, but the level of the key factor of vascular permeability and dilation of the TO-radical, the product of inducible NO synthase of endotheliocytes and arteriole myocytes, may remain high. Clinical and clinical-laboratory manifestations of microcirculatory disorders are characteristic, including shock, multiple organ dysfunction, certain signs of DIC. Fortunately, in such an obvious critical variant, the phase does not always manifest itself, more often in the form of mixed, "erased" variants that form interphase transitions, especially with the "pushing" option. As a rule, the phase develops critically for life after a very pronounced phase of primary phlogogenic shock with the "breakthrough" variant. At the level of the whole organism, the phase is characterized by a relative the dominance of the 3rd stage of cellular stress. The 4th phase – secondary phlogogenic shock, the repeated development of the hyperergic phase – is associated with the action of factors of secondary systemic damage, often manifests itself on the 5th-8th day of the development of a critical condition in a person with the "pushing" variant. Causes a high probability of developing life-threatening complications. Phase 5 – resolution – is characterized by relatively moderate hypercytokinemia, low probability of detecting markers of organ damage and dysfunction. The duration of the phase is from several days to several weeks. In its manifestations, it may resemble the phase of development of systemic inflammation. The phase is fixed in patients who have survived the most critical stage of

the development of systemic inflammation (phases 2-4), in a more favorable variant of the development of systemic inflammation, a transition from the 1st or 2nd immediately to the 5th resolution phase is possible, bypassing the 3rd and 4th phases of the gatherings.

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